# Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort

**Non-steroidal anti-inflammatory drugs (NSAIDs) use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: A matched prospective cohort study.**

Thomas M Drake[1], Cameron J Fairfield[1], Riinu Pius[1], Stephen R Knight[1], Lisa Norman[1], Michelle Girvan[2], Hayley E. Hardwick[3], Annemarie B Docherty[1], Ryan S Thwaites[4], Peter JM Openshaw[4], J Kenneth Baillie[5], Ewen M Harrison**[1], Malcolm G Semple**[3,6], for ISARIC4C Investigators*

1. Centre for Medical Informatics, Usher Institute, University of Edinburgh, Edinburgh, UK
2. Liverpool Clinical Trials Centre, University of Liverpool, Liverpool, UK
3. Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection, Veterinary and Ecological Sciences, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK
4. National Heart and Lung Institute, Imperial College London, UK
5. Roslin Institute, University of Edinburgh, Easter Bush, Edinburgh, UK
6. Department of Respiratory Medicine, Alder Hey Children's Hospital, Liverpool, UK

* = See names in supplementary authorship list.

** = Joint last authors

**Correspondence to:**

Professor Ewen M Harrison

Centre for Medical Informatics

Usher Institute

University of Edinburgh

EH16 4UX

**Email:** ewen.harrison@ed.ac.uk

**Telephone:** 0131 242 3614

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**Research in context**

*Evidence in context*

There have been anecdotal reports that use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to COVID-19 severity and poor outcomes. NSAIDs are an important analgesic class, used in the management of acute pain and rheumatological diseases. Several studies, in a variety of populations, have identified that patients taking NSAIDs who developSARS-CoV-2 infection are not at higher risk of hospitalisation or death. However, the populations included in these studies are frequently small, based on routine administrative data, or are drawn from community populations and hence have relatively low rates of SARS-CoV-2.

*Added value of this study*

This prospective, multicentre study from 255 UK healthcare facilities found that in patients who were hospitalised with COVID-19, those taking NSAIDs prior to admission had the same outcomes as those who did not. We did not find any differences in mortality, disease severity or in secondary outcomes including admission to critical care, use of ventilation, use of oxygen or presence of acute kidney injury.

*Implications of all the available evidence*

Those who are taking NSAIDs do not appear to have worse outcomes after COVID-19. Our prospective study contains the largest number of hospitalised COVID-19 patients, and significantly adds to the literature on the safety of NSAIDs and in-hospital outcomes. In the context of all the available evidence, NSAIDs do not appear to increase risk of hospitalisation or lead to worse in-hospital outcomes. NSAIDs are an important analgesic modality and have a vital opioid-sparing role in pain management. Patients and clinicians should be reassured by these findings that NSAIDs are likely safe in the context of the pandemic.

**Abstract**

**Background:** Reports suggested that existing use of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to increased severity in patients with COVID-19. NSAIDs are an important analgesic, particularly in those with rheumatologic disease, and are widely available to the public without prescription. Evidence from community studies, administrative data and in small studies of hospitalised patients suggest NSAIDs are not associated with worse outcomes.

**Methods:** Prospective, multicentre cohort study of patients hospitalised with COVID-19 in the UK between 17th January and 17th August 2020. The primary outcome was in-hospital mortality and secondary outcomes included disease severity at presentation, admission to critical care, receipt of invasive mechanical ventilation (IMV), receipt of noninvasive ventilation, use of supplementary oxygen and acute kidney injury. NSAID use was required to be within the 2 weeks prior to hospital admission. Logistic regression was used to estimate the effects of NSAIDs and adjust for confounding variables. Propensity score matching was used to further estimate effects of NSAIDS while accounting for covariate differences in populations. Effect estimates are presented as odds ratios (OR) with corresponding 95% confidence intervals.

**Results:** 72,179 patients were included in the clinical characterisation protocol study across 255 healthcare facilities. Of these, 4211 (5.8%) used NSAIDs prior to hospital admission. Following propensity score matching, balanced groups of NSAIDs and non-NSAIDs users were obtained (n = 4205 each). On admission, there were no significant differences in severity between exposure groups. After adjusting for explanatory variables, NSAID use was not associated with worse overall survival (matched OR 0·95, 95% CI 0·84 to 1·07, p = 0·352), critical care admission (matched OR 1·01, 95% CI 0·87 to 1·17, p = 0·890), requirement for invasive ventilation (matched OR 0·96, 95% CI 0·80 to 1·17, p = 0·694), requirement for noninvasive ventilation (matched OR 1·12, 95% CI 0·96 to 1·32, p = 0·143), requirement for oxygen (matched OR 1·00, 95% CI 0·89 to 1·12, p = 0·968) or occurrence of acute kidney injury (matched OR 1 ·08, 95% CI 0·92 to 1·26, p = 0·330).

**Conclusions and Relevance:** NSAID use is not associated with higher mortality or increased severity of COVID-19.

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## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) provide effective analgesia and are important in the treatment of inflammatory diseases. They form a part of the World Health Organisation's (WHO) pain ladder and have opioid sparing properties, supported by data from randomised controlled trials[1]. In March 2020, the French health ministry and media discussed unpublished data that use of NSAIDs increased the severity of COVID-19 infection[2,3]. Debate ensued, with some arguing NSAIDs should be avoided as a result[3–5]. This led to several regulatory authorities calling for urgent investigations between NSAIDs and COVID-19 severity[6].

In SARS-CoV-2 infection, there have been recent studies which did not find any associations between NSAID use, hospitalisation and worse outcomes[7–13]. These studies have been conducted in a variety of different populations. In the community, administrative data have not identified an increased risk of hospitalisation for patients taking NSAIDs[7,11,13]. Data on hospitalised patients is scarcer, but suggest that patients taking NSAIDs do not have worse outcomes to those who are not on NSAIDs[10–12]. Studies which focus on hospitalised cohorts have included patients from single centres or have small numbers of patients taking NSAIDs.

Studies of patients with non-SARS-CoV-2 respiratory infection have found associations between NSAID (including COX-2 inhibitors) use and increased rates of complications [14–19]. These studies found NSAID use was associated with higher rates of myocardial infarction, pleural empyema and longer length of hospital stay. However, outcomes from these pneumonia studies, such as empyema are often less of a concern in patients with SARS-CoV-2 infection. Recognised safety concerns with the use of NSAIDs including increased incidence of stroke, gastrointestinal bleeding, myocardial infarction, acute kidney injury and bleeding [14–17,20], which are more common in the elderly.

In contrast, a randomised control trial in the UK found ibuprofen reduced the symptom severity of acute respiratory tract infection of patients in the community[21]. In preclinical models, there is evidence that NSAIDs decrease pulmonary oedema, lessen endothelial leakiness, and reduce the severity of acute

respiratory distress syndrome (ARDS), leading to the suggestion they may be useful in the treatment of COVID-19 with at least one clinical trial currently underway[22–24].

The purpose of this study was to characterise the safety of NSAIDs and identify whether pre-existing NSAID use is associated with increased severity of COVID-19 disease.

## Methods

The International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) Clinical Characterisation Protocol (CCP) for Severe Emerging Infection was developed in 2009 and activated in response to the SARS-CoV-2 pandemic on 17th January 2020. This is an actively recruiting, prospective cohort study recruiting across England, Scotland, and Wales. The protocol, revision history, case report forms, study information and consent forms are available online (https://isaric4c.net). Data and analysis scripts are available on request. ISARIC-CCP-UK received ethical approval from the South Central - Oxford C Research Ethics Committee in England (Ref: 13/SC/0149), and by the Scotland A Research Ethics Committee (Ref: 20/SS/0028). The study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[25].

Patients of all ages from 17th January up to the 17th August 2020 admitted to hospital with a confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 disease were eligible for inclusion in this study. Confirmation of SARS-CoV-2 was performed using reverse-transcriptase polymerase chain reaction (RT-PCR) and was the only testing modality available in the UK during the reported study period. Highly suspected cases were eligible for inclusion, given that SARS-CoV-2 was an emergent pathogen at time of protocol activation. We excluded patients who did not have death or discharge outcomes available.

Data were collected by clinical research staff using a standardised case report form and entered into a Research Electronic Data Capture secure online database[26]. Data was captured across multiple timepoints, including at admission, during hospital stay (day 1, 3, 6 and 9) and discharge. Characteristics captured included age, biological sex, asthma, chronic cardiac disease, chronic haematologic disease, chronic kidney disease, chronic neurological disease, chronic non-asthmatic pulmonary disease, HIV/AIDs, malignancy, liver disease, obesity, rheumatologic disorder and smoking history. Physiological parameters at admission were captured, including components of the National Early Warning Score 2 (NEWS2) and the quick Sequential Organ Failure Assessment (qSOFA).

Current medication or medication taken within the past 2 weeks was recorded on hospital admission. The NSAID group was defined as patients taking generic or branded NSAIDs available within the UK, as determined using the NHS Technology Reference data Update Distribution Service, which were mapped to entered drug names within the study database. We defined exposure to NSAIDs as patients taking non-selective cyclooxygenase (COX) inhibitors or COX-2 specific inhibitors. Topical NSAID preparations were excluded. Aspirin was not considered an NSAID for the purposes of this analysis.

The primary outcome was in-hospital mortality (including palliative discharge). Secondary outcomes included admission to critical care (Level 3 Intensive Care Unit or Level 2 High Dependency Unit); use of invasive mechanical ventilation (IMV); use of non-invasive ventilation (NIV); use of supplementary oxygen; and occurrence of acute kidney injury (AKI). AKI was defined according to the KDIGO guidelines[27]. Patients who were admitted after 3rd August 2020 were excluded to avoid bias from patients with a long-stay or who had not had adequate time to accrue secondary outcomes.

*Statistical Analysis*

Categorical data are presented as frequency and percentages. Normally distributed variables were summarised as mean (SD, standard deviation) and non-normally distributed variables as median (IQR, interquartile range). The Chi-square test was used to compare categorical data, except for where expected cell counts were 5 or fewer, where Fisher's exact test was used. Continuous variables were compared using Welch's T-test or the Kruskall-Wallis test, depending on the distribution of data.

Propensity score matching was used to estimate the treatment effect of NSAIDs while accounting for covariate imbalance. This was done using a multistep approach. First, multiple imputation by chained equations was performed using available explanatory variables (age, sex, diabetes (type 1 or type 2), chronic cardiac disease, chronic renal disease, obesity, chronic pulmonary disease, ethnicity, dementia, and rheumatological disease) and outcomes (5 imputed datasets with 5 iterations per dataset; distributions checked graphically, and convergence confirmed). Second, logistic regression was used to determine the log odds of NSAID use (propensity scores) using the variables stated above. For logistic regression models, patient level explanatory variables were entered as fixed effects and in unmatched

models, hospital was used as a random effect. We did not use random effects for matched models to ensure we could match on clinical characteristics, rather than restrict matches to within each centre. Following this, propensity score matching was performed within each imputed dataset where patients on NSAIDs were matched 1:1 with their nearest neighbour not taking NSAIDs[28]. Balance was determined using standardised mean differences. Fourth, effects estimates were determined, and results pooled using Rubin's rules[29]. Effect estimates are presented as odds ratios (OR) for binary outcome data, alongside their corresponding 95% confidence intervals. Imputed and matched data are presented as pooled models.

For unmatched models, clinically plausible variables associated with NSAID use and clinical outcomes were incorporated into the modelling approach. These variables included age, sex, presence of chronic cardiac disease, chronic pulmonary disease, diabetes, obesity, chronic renal disease, rheumatological disease and dementia. First order interactions were checked prior to final model selection which was guided by minimisation of the Akaike Information Criterion (AIC). Statistical significance was taken at the level of $P<0{\cdot}05$. Data were analysed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, AUT) using the tidyverse, finalfit, mice, MatchThem, cobalt and matchit packages.

*Sensitivity analysis*

We performed a sensitivity analysis including non-ibuprofen NSAIDs only, as these usually require a prescription in the UK and are more likely to be taken longer term than ibuprofen. We also undertook an analysis confined to patients with rheumatic disease, as this group are likely to be on long-term NSAIDs compared to others who may be taking NSAIDs for short-term analgesia.

*Role of the funding source*

The study sponsors and funders had no role in the study design, collection, analysis, data interpretation or report writing. TMD, RP, LN, JKB, ABD, MGS and EMH had access to the raw data. The corresponding author had full access to all data and the final responsibility to submit for publication.

## Results

*Patient characteristics*

Up to 10th August 2020, 78,674 patients were enrolled across 255 healthcare facilities in England, Scotland and Wales, representing around 60% of the total number of people admitted to hospital with COVID-19 over that time period. Of these, 72,179 patients had death outcomes available for matching. There did not appear to be large differences in distribution of explanatory variables by missing mortality outcome (appendix table 1). In this cohort 4211 (5·8%) were recorded as taking systemic NSAIDs prior to admission. In the unmatched data (table 1 and appendix table S2), patients who received NSAIDs were younger, more likely to be female and were significantly more likely to have pre-existing rheumatological disease. Propensity score matching produced balanced, well-matched treatment groups for each set of imputed and pooled models (appendix figure 1 and appendix tables S3-8).

*Disease severity at presentation*

On presentation to hospital, matched patients on NSAIDs had comparable qSOFA and NEWS2 scores to those who did not receive NSAIDs (figure 2). Use of NSAIDs was not associated with any differences in physiological scores or physiological parameters (table 3).

*Mortality and NSAID use*

The mortality rate was 30·4% (1279/4211) in the NSAIDs group and 31·3% (21,256/67,698) in the no NSAIDs group (supplementary figure 2). Unmatched outcomes including in-hospital mortality in our cohort are shown in table 2, where there were no significant differences in outcomes between NSAID and non-NSAID users. In a sensitivity analysis of patients admitted to hospital at least 7 days after symptom onset who were taking NSAIDs (19,734 /72,179) matched to patients not taking NSAIDs presenting in a similar time frame, there was no difference in survival (matched OR 1·11, 95% CI 0·88 to 1·39, p = 0·374). In patients with rheumatologic disease (7,614/72,179), use of NSAIDs did not appear to be associated with increased mortality (matched OR 0·90, 95% CI 0·68 to 1·19, P = 0·444).

*Secondary outcomes and NSAID use*

In the unmatched cohort NSAID users were slightly more likely to require non-invasive ventilation and sustain acute kidney injury (table 2). After matching, those taking NSAIDs were no more likely to require critical care, invasive mechanical ventilation, noninvasive ventilation or supplementary oxygen (table 3 and supplementary figure 2). When we did a sensitivity analysis, excluding those who died, our direction of findings did not change, and we did not observe any increase or decrease in associations between NSAIDs and any of the secondary outcomes (appendix table S9). A further two sensitivity analyses were performed to ensure around the secondary outcomes. First, we combined death and critical care outcomes together. Second, we went on to look at mortality in the population who did not require critical care. These analyses found showed no association between NSAIDs and the chances of death or admission to critical care when these were combined (OR 0·94, 95% CI 0·83 to 1·06, p = 0·278) nor any association with death in patients who were not admitted to critical care (OR 0·92, 95% CI 0·82 to 1·03, p = 0·156).

*Differences in types of NSAIDs*

The commonest type of NSAIDs in use was ibuprofen, followed by "other" NSAIDs, diclofenac/ketorolac/naproxen, oxicams, and finally COX-2 inhibitors. There were no significant differences in mortality by type of NSAID (appendix table S10). As a sensitivity analysis to explore whether NSAIDs associated with longer term use had a different safety profile compared with ibuprofen, we created matched groups to compare ibuprofen with no NSAID use, and ibuprofen with other NSAIDs. Use of ibuprofen was not significantly associated with increased mortality compared with those on no NSAIDs (matched OR 0·90, 95% CI 0·71 to 1·13, P = 0·359, supplementary table S11) or any other NSAID (matched OR 0·82, 95% CI 0·66 to 1.03, p = 0·082, supplementary table S12).

## Discussion

In this study of 78,674 patients admitted to hospital with COVID-19, those who were taking NSAIDs did not have more severe disease than patients who were not on NSAIDs. Mortality, critical care admission, respiratory support and acute kidney injury were also comparable across matched NSAID-treatment groups. We could not find evidence of harm NSAID use in patients admitted to hospital with severe COVID-19.

Early in the pandemic, questions were raised around the safety of NSAIDs in patients with COVID-19, with suggestion that NSAIDs were leading to severe disease in a some patients [2,30,31]. Our data show patients taking NSAIDs did not have more severe symptoms or worse outcomes than those not taking NSAIDs. These data agree with community studies demonstrating NSAID users do not have higher rates of hospitalisation and smaller studies of in-hospital outcomes, which found NSAID use is not associated with worse outcomes. A recent, propensity matched data linkage study of patients with osteoarthritis taking NSAIDs in the community setting by Chandan et al., found no difference in the risk of developing COVID-19 or dying from it[13]. Compared with our data, and previous studies our consortium has published, the Chandan et al. study did not find any differences in risk factors for mortality following COVID-19, which is likely reflected by the very small numbers of patients with COVID-19 in their study[13]. Compared to the existing literature, we understand our study is the largest study of in-hospital outcomes of patients with COVID-19. In light of all the evidence, if there was an extreme effect of NSAIDs on COVID-19 outcomes or severity it would have likely been observed in one or more of the studies that have been performed, including ours.

This is the largest prospective study of patients admitted to hospital in the world with COVID-19. We were able to collect real-time data on patients to study their outcomes and collect detailed comorbidity data. As part of this data collection, clinical research staff collected data on medications patients had been prescribed or were taking currently, or within the past 14 days. These data are otherwise challenging to obtain from routine sources of healthcare data. Whilst we have currently captured data on patients admitted to hospital with COVID-19, this only represents 60% of the hospitalised UK population over the course of the pandemic. This study did not capture patients who had disease which

could be managed in the community, or indeed disease progressing to palliation in the community without hospital admission. Despite this, it would be expected that most patients who had severe COVID-19 disease would be admitted to hospital and thus captured in our data. A further potential weakness of our study is the lack of information on the indication for NSAIDs and duration of use. This makes it difficult to know whether individuals were taking NSAIDs for long-term conditions, or symptomatic relief for COVID-19 symptoms. Similarly, it is unknown whether patients continued NSAIDs during their inpatient admission. Therefore, we are unable to make any recommendations on whether NSAIDs should be continued on admission to hospital. To address this, we performed a sensitivity analysis comparing ibuprofen to no NSAIDs or use of other non-ibuprofen NSAIDs, as ibuprofen use is most likely to be short-term. There was no increase in worse outcomes in the ibuprofen group compared with those who did not use NSAIDs. Similarly, it is possible that as older patients who are at greatest risk of adverse outcomes from COVID-19 are less likely to be taking NSAIDs than other, more healthy and fit populations, our matching may not have incorporated this patient group fully. But seeing as these patients are less likely to be taking NSAIDs and the safety debate is around younger populations, this is unlikely affect our results and their relevance to clinical practice.

There are several other important limitations to our study that must be considered. First, the most used NSAID was ibuprofen, which may not be generalisable to every country. Different NSAIDs are well-known to have different side-effect profiles, therefore clinical trials of a specific compound may not be generalisable to an entire drug class[32]. In addition to this, our data did not contain drug dosages or adherence data, so we were unable to model dose-response. Secondly, although our study captured data on the majority of patients hospitalised with COVID-19 in the UK over the time period it was conducted, a few centres did not participate. However, our data is concordant with other datasets focussed on smaller populations within our study, such as data from the Intensive Care National Audit and Research Centre (ICNARC)[33]. Therefore, we consider our data is meaningful and is useful to help answer important clinical questions in patients with COVID-19. Another limitation that should be considered is that in order to obtain the best possible matches for patients receiving NSAIDs, we did not include date of admission as a matching variable. Mortality for hospitalised patients over the course

of the pandemic has decreased, but this is unlikely to have affected our conclusions given the time period we conducted our study over was limited largely to the first UK wave of infection. Finally, our data lacks a non-SARS-CoV-2 comparator group to provide a temporal comparison with other critical illness or respiratory conditions. Future research may wish to include a comparator group to see if NSAIDs modify or moderate outcomes of interest in COVID-19 compared with other illnesses.

Although use of NSAIDs could, in theory, be beneficial in patients with COVID-19, we did not identify any evidence to support this. Clinical studies have suggested release of proinflammatory mediators in COVID-19, including IL-1β, IL-6 and MCP-1, are associated with more severe COVID-19 disease[34,35]. Preclinical studies, in non-COVID-19 models, have found release of these cytokines can be inhibited by treatment with NSAIDs and has led to discussion around whether NSAIDs may be useful as a therapy for COVID-19[23,36,37]. In these studies, NSAIDs have been found to suppress IL-6 production and expression through a variety of mechanisms, including suppression of prostaglandin E2 which upregulates production of IL-6 and IL-8[36,37]. Studies in bronchial epithelium have found that treatment with NSAIDs reduces expression of inflammatory mediators, including IL-6[36]. A clinical trial of dexamethasone, which also has been shown to modulate inflammation[38], albeit likely through a separate mechanism, has been shown to reduce mortality in COVID-19 patients. Other immunomodulatory therapies are currently being trialled, including the IL-6 inhibitor Tocilizumab. Results from the REMAP-CAP study, currently only available as a press release, has identified that Tocilizumab may reduce requirement for organ support and improve survival, with further trials underway[39–41]. In addition to these trials, a randomised trial of ibuprofen in patients with COVID-19 is also taking place[23].

For clinicians and patients, our findings should provide reassurance that NSAIDs can be used as indicated in the community without increasing the risk of severity of COVID-19. Our study did not capture whether NSAIDs were continued in-hospital, so we cannot make any recommendations on whether these should be withheld or continued. There are important groups of patients who rely on NSAIDs for pain relief, including those with inflammatory joint diseases, bone pain, gout, postoperative pain, and menstrual pain, who would otherwise have few non-opioid options for pain relief. Taken

together, clinicians should continue to prescribe and manage NSAIDs in the same way as before the SARS-CoV-2 pandemic began.

Future research in this area should focus on whether NSAIDs sufficiently modulate inflammation in COVID-19, by using both basic science and clinical approaches which use appropriate outcomes which are directly measured. If benefit or harm is identified, finding the cellular mechanisms responsible for these effects will be important to inform the biological understanding of COVID-19 disease. Finally, including arms that compare NSAIDs to alternative analgesics should be considered, to provide evidence for clinicians and patients on the risks associated with alternative medications. Policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity considering our study. In conclusion, NSAID use is not associated with worse outcomes in hospitalised patients with COVID-19.

**Data sharing statement**

Data, protocols and all documentation around this analysis will be made available to academic researchers following authorisation from the independent data access and sharing committee: https://isaric4c.net/sample_access/.

**Conflicts of interest**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the National Institute for Health Research (NIHR), the Medical Research Council (MRC), the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool, NIHR HPRU in Respiratory Infections at Imperial College London, NIHR Biomedical Research Centre at Imperial College London, and NIHR Clinical Research Network for the submitted work; ABD reports grants from Department of Health and Social Care (DHSC), during the conduct of the study, grants from Wellcome Trust, outside the submitted work; PJMO reports personal fees from consultancies and from European Respiratory Society, grants from MRC, MRC Global Challenge Research Fund, EU, NIHR BRC, MRC/GSK, Wellcome Trust, NIHR (Health Protection Research Unit (HPRU) in Respiratory Infection), and is NIHR senior investigator outside the submitted work; his role as President of the British Society for Immunology was unpaid but travel and accommodation at some meetings was provided by the Society; JKB reports grants from MRC UK; MGS reports grants from DHSC NIHR UK, grants from MRC UK, grants from HPRU in Emerging and Zoonotic Infections, University of Liverpool, during the conduct of the study, other from Integrum Scientific LLC, Greensboro, NC, USA, outside the submitted work. TMD, CJF, RP, SRK, LN, MG, HEH, RST and EMH all declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

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**Table 1 –** Unmatched patient characteristics by NSAID use

| | Total N | | No NSAIDs N = 67968 | NSAIDs N = 4211 | p |
|---|---|---|---|---|---|
| Age on admission (years) | 71987 | Mean (SD) | 70.2 (18.4) | 70.1 (18.7) | 0.765* |
| Sex at Birth | 71915 | Male | 38151 (56.1) | 2255 (53.6) | 0.001 |
| | | Female | 29564 (43.5) | 1945 (46.2) | |
| | | (Missing) | 253 (0.4) | 11 (0.3) | |
| Ethnicity | 64123 | Asian | 3708 (5.5) | 230 (5.5) | 0.116 |
| | | Black | 2358 (3.5) | 118 (2.8) | |
| | | White | 50124 (73.7) | 3109 (73.8) | |
| | | Other | 4201 (6.2) | 275 (6.5) | |
| | | (Missing) | 7577 (11.1) | 479 (11.4) | |
| Smoking | 43585 | Yes | 3588 (5.3) | 228 (5.4) | <0.001 |
| | | Never Smoked | 22896 (33.7) | 1394 (33.1) | |
| | | Former Smoker | 14428 (21.2) | 1051 (25.0) | |
| | | (Missing) | 27056 (39.8) | 1538 (36.5) | |
| Chronic cardiac disease | 67454 | No | 42831 (63.0) | 2557 (60.7) | <0.001 |
| | | Yes | 20588 (30.3) | 1478 (35.1) | |
| | | (Missing) | 4549 (6.7) | 176 (4.2) | |
| Chronic kidney disease | 66964 | No | 51800 (76.2) | 3237 (76.9) | 0.042 |
| | | Yes | 11167 (16.4) | 760 (18.0) | |
| | | (Missing) | 5001 (7.4) | 214 (5.1) | |
| Chronic pulmonary disease (not asthma) | 67171 | No | 51933 (76.4) | 3219 (76.4) | 0.003 |
| | | Yes | 11232 (16.5) | 787 (18.7) | |
| | | (Missing) | 4803 (7.1) | 205 (4.9) | |
| Obesity (as defined by clinical staff) | 60199 | No | 49993 (73.6) | 3039 (72.2) | <0.001 |
| | | Yes | 6590 (9.7) | 577 (13.7) | |
| | | (Missing) | 11385 (16.8) | 595 (14.1) | |
| Diabetes | 65135 | No Diabetes | 46728 (68.8) | 2881 (68.4) | 0.189 |
| | | Diabetes with complications | 4484 (6.6) | 299 (7.1) | |
| | | Diabetes without complications | 10150 (14.9) | 593 (14.1) | |
| | | (Missing) | 6606 (9.7) | 438 (10.4) | |
| Rheumatologic disorder | 66228 | No | 55469 (81.6) | 3145 (74.7) | <0.001 |
| | | Yes | 6809 (10.0) | 805 (19.1) | |
| | | (Missing) | 5690 (8.4) | 261 (6.2) | |
| Dementia | 66788 | No | 51980 (76.5) | 3368 (80.0) | <0.001 |
| | | Yes | 10845 (16.0) | 595 (14.1) | |
| | | (Missing) | 5143 (7.6) | 248 (5.9) | |

NSAIDs – Non-steroidal anti-inflammatory drugs, SD – Standard Deviation. All tests Chi-square unless denoted by * where Welch's two-sample t-test used.

**Table 2** – Unmatched outcomes by NSAID use

| | Total number of patients | Missing number of patients | | No NSAIDs N = 67968 | NSAIDs N = 4211 | p |
|---|---|---|---|---|---|---|
| Mortality | 72179 | 0 | No | 46712 (68.7) | 2932 (69.6) | 0.227 |
| | | | Yes | 21256 (31.3) | 1279 (30.4) | |
| Critical Care Admission | 70955 | 1224 | No | 57507 (86.1) | 3599 (85.7) | 0.467 |
| | | | Yes | 9250 (13.9) | 599 (14.3) | |
| Invasive Ventilation | 69972 | 2207 | No | 60254 (91.5) | 3821 (91.9) | 0.396 |
| | | | Yes | 5562 (8.5) | 335 (8.1) | |
| Noninvasive Ventilation | 69818 | 2361 | No | 55809 (85.0) | 3452 (83.3) | 0.005 |
| | | | Yes | 9867 (15.0) | 690 (16.7) | |
| Supplemental Oxygen | 70124 | 2055 | No | 22826 (34.6) | 1420 (34.2) | 0.620 |
| | | | Yes | 43147 (65.4) | 2731 (65.8) | |
| Acute Kidney Injury | 68228 | 3951 | No | 48258 (75.1) | 2945 (73.6) | 0.034 |
| | | | Yes | 15970 (24.9) | 1055 (26.4) | |

NSAIDs – Non-steroidal anti-inflammatory drugs**.** All tests Chi-square.

**Table 3 –** Outcomes following propensity score matching between those using NSAIDs prior to admission and those not using NSAIDs.

| | Outcome | Dependent variable | Patients with available data (matched 1:1) | Effect estimate |
|---|---|---|---|---|
| | | | | Matched odds ratio (95% CI, p-value) |
| In-hospital mortality | No NSAIDs | | | 1 (Reference level) |
| | NSAIDs | In-hospital mortality | (4205:4205) | 0.95 (0.84 to 1.07, p = 0.352) |
| | | | | Matched odds ratio (95% CI, p-value) |
| Secondary outcomes | No NSAIDs | | | 1 (Reference level) |
| | NSAIDs | Critical care admission | (4198:4198) | 1.01 (0.87 to 1.17, p = 0.890) |
| | | Invasive ventilation | (4156:4156) | 0.96 (0.80 to 1.17, p = 0.694) |
| | | Noninvasive ventilation | (4142:4142) | 1.12 (0.96 to 1.32, p = 0.143) |
| | | Oxygen | (4151:4151) | 1.00 (0.89 to 1.12, p = 0.968) |
| | | Acute Kidney Injury | (4000:4000) | 1.08 (0.92 to 1.26, p = 0.330) |
| | | | | Mean difference (95% CI, p-value) |
| Severity on admission | Physiological scores | qSOFA score | (3793:3793) | -0.02 (-0.06 to 0.02, p = 0.423) |
| | | NEWS score | (3721:3721) | -0.08 (-0.30 to 0.14, p = 0.461) |
| | Physiological parameters | Heart rate | (4102:4102) | -0.40 (-1.39 to 0.59, p = 0.432) |
| | | Respiratory rate | (4096:4096) | -0.17 (-0.66 to 0.32, p = 0.478) |
| | | SpO2 | (4076:4076) | -0.00 (-0.27 to 0.26, p = 0.980) |
| | | Systolic blood pressure | (4085:4085) | 1.09 (-0.07 to 2.25, p = 0.066) |
| | | Diastolic blood pressure | (4071:4071) | -0.21 (-0.93 to 0.51, p = 0.563) |

CI – Confidence Interval, qSOFA – quick Sequential Organ Failure Assessment, SpO2 – saturation of peripheral oxygen, NSAIDs – non-steroidal anti-inflammatory drugs.

**Figures**

**Figure 1** – Study inclusion flowchart

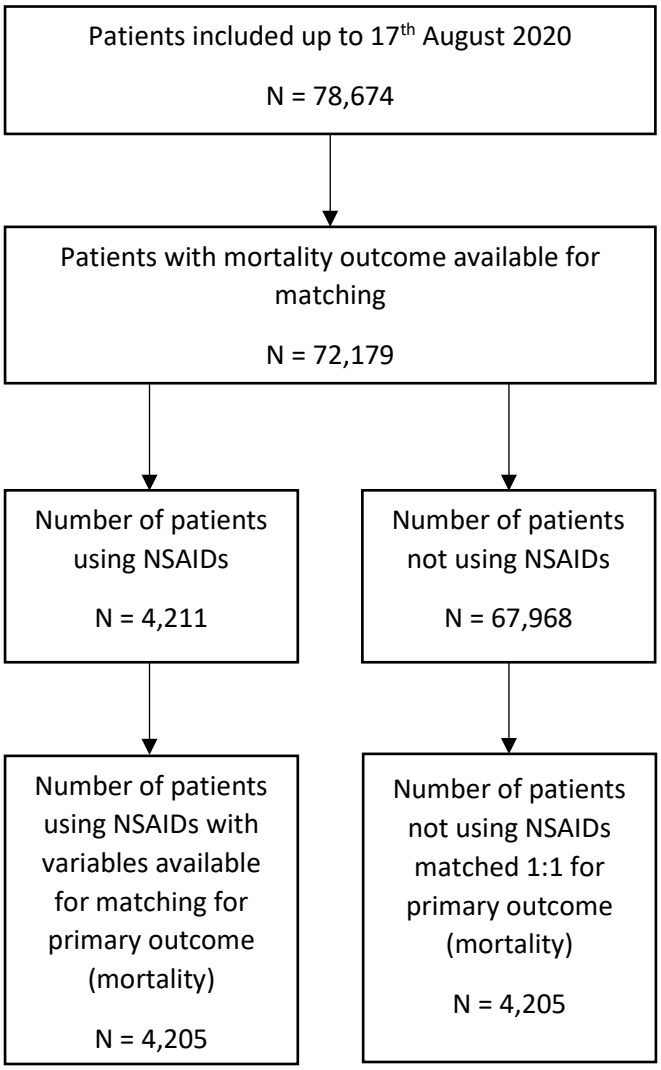
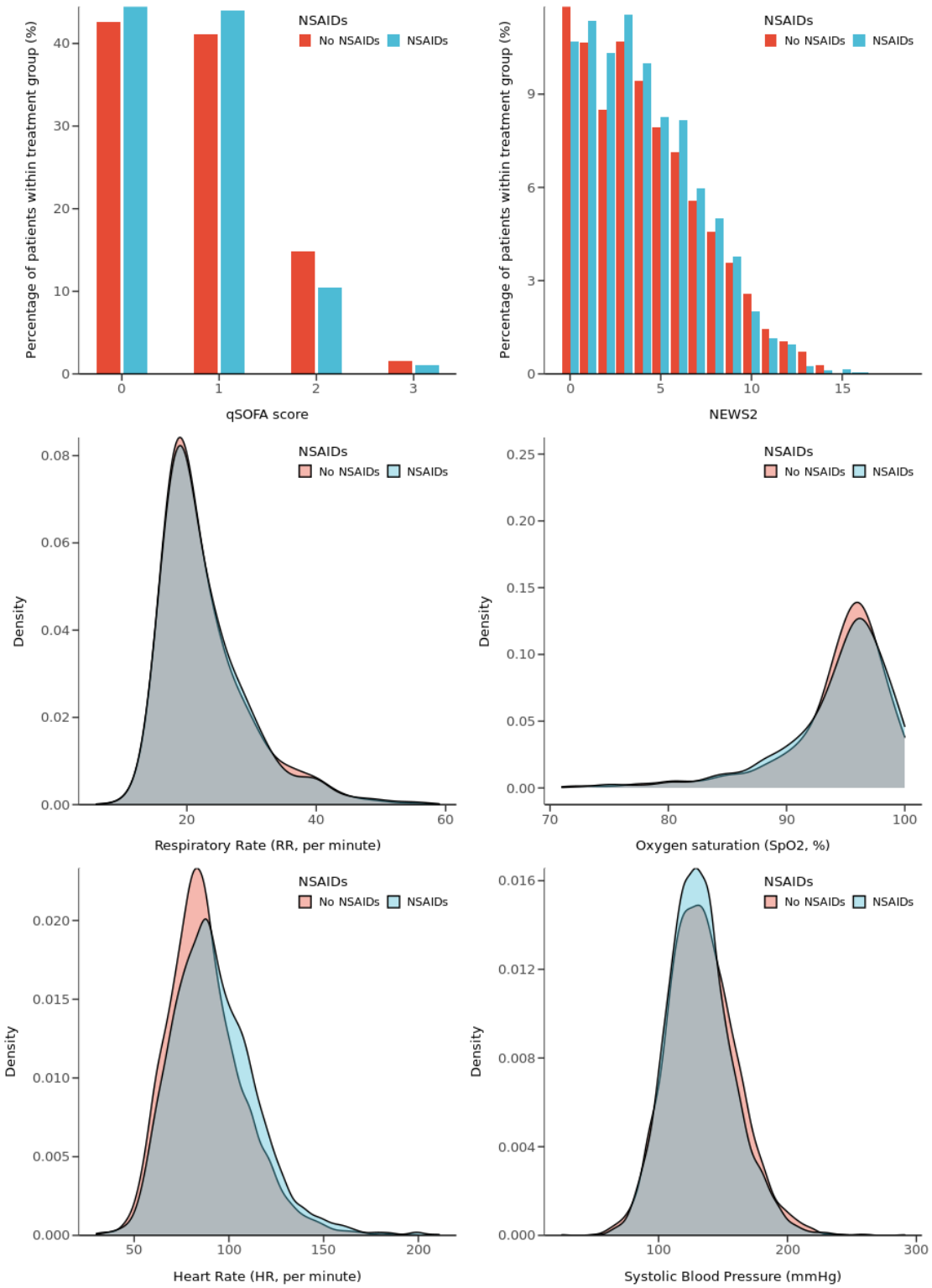


**Figure 2** – Distribution of physiological parameters on admission by NSAID use in matched, complete case cohort (3708 NSAIDs users, 3708 matched controls).




BP – Blood pressure, NEWS – National Early Warning Score 2, NSAIDs – Non-steroidal anti-inflammatory drugs, qSOFA – Quick Sequential Organ Failure Assessment, SpO2 – Peripheral Saturation of Oxygen.

## Appendix

**Table S1 –** Missing data analysis

| Missing data analysis: Death | | Not missing | Missing |
|---|---|---|---|
| Age (years) | <50 | 9938 (13.8) | 416 (16.7) |
| | 50-69 | 19534 (27.1) | 679 (27.3) |
| | 70-79 | 16099 (22.4) | 557 (22.4) |
| | 80+ | 26419 (36.7) | 838 (33.7) |
| Sex | Male | 40406 (56.2) | 1414 (56.4) |
| | Female | 31509 (43.8) | 1093 (43.6) |
| Chronic Cardiac Disease | No | 45388 (67.3) | 1147 (66.8) |
| | Yes | 22066 (32.7) | 569 (33.2) |
| Chronic Pulmonary Disease | No | 55152 (82.1) | 1382 (81.5) |
| | Yes | 12019 (17.9) | 314 (18.5) |
| Diabetes | No Diabetes | 49609 (76.2) | 1255 (76.3) |
| | Diabetes with complications | 4783 (7.3) | 110 (6.7) |
| | Diabetes without complications | 10743 (16.5) | 279 (17.0) |
| Obesity | No | 53032 (88.1) | 1380 (90.1) |
| | Yes | 7167 (11.9) | 151 (9.9) |
| Chronic Kidney Disease | No | 55037 (82.2) | 1389 (82.4) |
| | Yes | 11927 (17.8) | 296 (17.6) |
| Rheumatic Disease | No | 58614 (88.5) | 1506 (91.3) |
| | Yes | 7614 (11.5) | 143 (8.7) |
| Dementia | No | 55348 (82.9) | 1414 (84.7) |
| | Yes | 11440 (17.1) | 255 (15.3) |

**Table S2 –** Overall characteristics of study cohort

| | Total number of patients | Missing data | | |
|---|---|---|---|---|
| Total N (%) | | | | 72179 (100.0) |
| Age on admission (years) | 71987 | 192 | Mean (SD) | 70.2 (18.4) |
| Sex at Birth | 71915 | 264 | Male | 40406 (56.2) |
| | | | Female | 31509 (43.8) |
| Chronic cardiac disease | 67454 | 4725 | No | 45388 (67.3) |
| | | | Yes | 22066 (32.7) |
| Chronic kidney disease | 66964 | 5215 | No | 55037 (82.2) |
| | | | Yes | 11927 (17.8) |
| Chronic pulmonary disease (not asthma) | 67171 | 5008 | No | 55152 (82.1) |
| | | | Yes | 12019 (17.9) |
| Obesity (as defined by clinical staff) | 60199 | 11980 | No | 53032 (88.1) |
| | | | Yes | 7167 (11.9) |
| Diabetes | 65135 | 7044 | Diabetes with complications | 4783 (7.3) |
| | | | Diabetes without complications | 10743 (16.5) |
| | | | No Diabetes | 49609 (76.2) |
| Rheumatologic disorder | 66228 | 5951 | No | 58614 (88.5) |
| | | | Yes | 7614 (11.5) |
| Dementia | 66788 | 5391 | No | 55348 (82.9) |
| | | | Yes | 11440 (17.1) |

**Table S3**- Summary of matched imputed datasets for mortality outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 537 (12.77) | 540 (12.84) |
| | 50-69 | 1199 (28.51) | 1198 (28.50) |
| | 70-79 | 958 (22.78) | 954 (22.69) |
| | 80+ | 1512 (35.95) | 1512 (35.97) |
| Sex at birth | Female | 2256 (53.65) | 2255 (53.63) |
| | Male | 1949 (46.35) | 1950 (46.37) |
| Chronic Cardiac Disease | No | 2667 (63.42) | 2668 (63.45) |
| | Yes | 1538 (36.58) | 1537 (36.55) |
| Diabetes Mellitus | No Diabetes | 3196 (76.00) | 3194 (75.96) |
| | Diabetes with complications | 343 (8.16) | 346 (8.23) |
| | Diabetes without complications | 666 (15.84) | 665 (15.81) |
| Obesity | No | 3537 (84.11) | 3536 (84.09) |
| | Yes | 668 (15.89) | 669 (15.91) |
| Chronic Kidney Disease | No | 3402 (80.90) | 3400 (80.86) |
| | Yes | 803 (19.10) | 805 (19.14) |
| Rheumatic disease | No | 3339 (79.41) | 3339 (79.41) |
| | Yes | 866 (20.59) | 866 (20.59) |
| Dementia | No | 3571 (84.92) | 3568 (84.85) |
| | Yes | 634 (15.08) | 637 (15.15) |
| Outcome (not included in matching) | | | |
| Death | Alive | 2881 (68.51) | 2932 (69.73) |
| | Died | 1324 (31.49) | 1273 (30.27) |

**Table S4-** Summary of matched imputed datasets for critical care outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 533 (12.70) | 537 (12.79) |
| | 50-69 | 1200 (28.59) | 1199 (28.55) |
| | 70-79 | 954 (22.73) | 954 (22.72) |
| | 80+ | 1510 (35.98) | 1509 (35.94) |
| Sex at birth | Male | 2254 (53.69) | 2253 (53.67) |
| | Female | 1944 (46.31) | 1945 (46.33) |
| Chronic Cardiac Disease | No | 2660 (63.36) | 2662 (63.41) |
| | Yes | 1538 (36.64) | 1536 (36.59) |
| Diabetes Mellitus | No Diabetes | 3186 (75.89) | 3186 (75.89) |
| | Diabetes with complications | 341 (8.12) | 344 (8.19) |
| | Diabetes without complications | 671 (15.98) | 668 (15.91) |
| Obesity | No | 3528 (84.04) | 3526 (83.99) |
| | Yes | 670 (15.96) | 672 (16.01) |
| Chronic Kidney Disease | No | 3386 (80.66) | 3386 (80.66) |
| | Yes | 812 (19.34) | 812 (19.34) |
| Rheumatic disease | No | 3337 (79.49) | 3337 (79.49) |
| | Yes | 861 (20.51) | 861 (20.51) |
| Dementia | No | 3567 (84.97) | 3562 (84.85) |
| | Yes | 631 (15.03) | 636 (15.15) |
| Outcome (not included in matching) | | | |
| Critical care admission | No | 3604 (85.85) | 3599 (85.73) |
| | Yes | 594 (14.15) | 599 (14.27) |

**Table S5-** Summary of matched imputed datasets for invasive ventilation outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 529 (12.73) | 533 (12.82) |
| | 50-69 | 1190 (28.63) | 1188 (28.59) |
| | 70-79 | 945 (22.74) | 946 (22.76) |
| | 80+ | 1492 (35.90) | 1489 (35.83) |
| Sex at birth | Male | 2229 (53.63) | 2227 (53.59) |
| | Female | 1927 (46.37) | 1929 (46.41) |
| Chronic Cardiac Disease | No | 2639 (63.50) | 2643 (63.59) |
| | Yes | 1517 (36.50) | 1513 (36.41) |
| Diabetes Mellitus | No Diabetes | 3152 (75.84) | 3153 (75.87) |
| | Diabetes with complications | 344 (8.28) | 344 (8.28) |
| | Diabetes without complications | 660 (15.88) | 659 (15.86) |
| Obesity | No | 3490 (83.97) | 3488 (83.93) |
| | Yes | 666 (16.03) | 668 (16.07) |
| Chronic Kidney Disease | No | 3357 (80.77) | 3356 (80.75) |
| | Yes | 799 (19.23) | 800 (19.25) |
| Rheumatic disease | No | 3309 (79.62) | 3308 (79.60) |
| | Yes | 847 (20.38) | 848 (20.40) |
| Dementia | No | 3533 (85.01) | 3528 (84.89) |
| | Yes | 623 (14.99) | 628 (15.11) |
| Outcome (not included in matching) | | | |
| Invasive mechanical ventilation | No | 3805 (91.55) | 3821 (91.94) |
| | Yes | 351 (8.45) | 335 (8.06) |

**Table S6-** Summary of matched imputed datasets for non-invasive ventilation outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 528 (12.75) | 532 (12.84) |
| | 50-69 | 1186 (28.63) | 1183 (28.56) |
| | 70-79 | 945 (22.82) | 945 (22.82) |
| | 80+ | 1483 (35.80) | 1482 (35.78) |
| Sex at birth | Male | 2226 (53.74) | 2224 (53.69) |
| | Female | 1916 (46.26) | 1918 (46.31) |
| Chronic Cardiac Disease | No | 2627 (63.42) | 2628 (63.45) |
| | Yes | 1515 (36.58) | 1514 (36.55) |
| Diabetes Mellitus | No Diabetes | 3135 (75.69) | 3133 (75.64) |
| | Diabetes with complications | 341 (8.23) | 344 (8.31) |
| | Diabetes without complications | 666 (16.08) | 665 (16.06) |
| Obesity | No | 3479 (83.99) | 3478 (83.97) |
| | Yes | 663 (16.01) | 664 (16.03) |
| Chronic Kidney Disease | No | 3341 (80.66) | 3341 (80.66) |
| | Yes | 801 (19.34) | 801 (19.34) |
| Rheumatic disease | No | 3294 (79.53) | 3294 (79.53) |
| | Yes | 848 (20.47) | 848 (20.47) |
| Dementia | No | 3520 (84.98) | 3516 (84.89) |
| | Yes | 622 (15.02) | 626 (15.11) |
| Outcome (not included in matching) | | | |
| Noninvasive ventilation | No | 3496 (84.40) | 3452 (83.34) |
| | Yes | 646 (15.60) | 690 (16.66) |

**Table S7-** Summary of matched imputed datasets for supplemental oxygen outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 530 (12.77) | 533 (12.84) |
| | 50-69 | 1190 (28.67) | 1187 (28.60) |
| | 70-79 | 943 (22.72) | 943 (22.72) |
| | 80+ | 1487 (35.83) | 1488 (35.85) |
| Sex at birth | Male | 2237 (53.89) | 2237 (53.89) |
| | Female | 1914 (46.11) | 1914 (46.11) |
| Chronic Cardiac Disease | No | 2635 (63.48) | 2635 (63.48) |
| | Yes | 1516 (36.52) | 1516 (36.52) |
| Diabetes Mellitus | No Diabetes | 3146 (75.79) | 3145 (75.76) |
| | Diabetes with complications | 341 (8.21) | 344 (8.29) |
| | Diabetes without complications | 664 (16.00) | 662 (15.95) |
| Obesity | No | 3483 (83.91) | 3482 (83.88) |
| | Yes | 668 (16.09) | 669 (16.12) |
| Chronic Kidney Disease | No | 3354 (80.80) | 3354 (80.80) |
| | Yes | 797 (19.20) | 797 (19.20) |
| Rheumatic disease | No | 3295 (79.38) | 3295 (79.38) |
| | Yes | 856 (20.62) | 856 (20.62) |
| Dementia | No | 3534 (85.14) | 3529 (85.02) |
| | Yes | 617 (14.86) | 622 (14.98) |
| Outcome (not included in matching) | | | |
| Supplemental oxygen | No | 1419 (34.18) | 1420 (34.21) |
| | Yes | 2732 (65.82) | 2731 (65.79) |

**Table S8-** Summary of matched imputed datasets for acute kidney injury outcome

| | | No NSAIDs | NSAIDs |
|---|---|---|---|
| Age (years) | <50 | 420 (10.50) | 423 (10.57) |
| | 50-69 | 1170 (29.25) | 1168 (29.20) |
| | 70-79 | 936 (23.40) | 936 (23.40) |
| | 80+ | 1474 (36.85) | 1473 (36.83) |
| Sex at birth | Male | 2163 (54.07) | 2161 (54.02) |
| | Female | 1837 (45.92) | 1839 (45.98) |
| Chronic Cardiac Disease | No | 2506 (62.65) | 2508 (62.70) |
| | Yes | 1494 (37.35) | 1492 (37.30) |
| Diabetes Mellitus | No Diabetes | 3018 (75.45) | 3019 (75.48) |
| | Diabetes with complications | 332 (8.30) | 333 (8.33) |
| | Diabetes without complications | 650 (16.25) | 648 (16.20) |
| Obesity | No | 3352 (83.80) | 3351 (83.78) |
| | Yes | 648 (16.20) | 649 (16.23) |
| Chronic Kidney Disease | No | 3219 (80.47) | 3217 (80.42) |
| | Yes | 781 (19.53) | 783 (19.57) |
| Rheumatic disease | No | 3168 (79.20) | 3167 (79.17) |
| | Yes | 832 (20.80) | 833 (20.82) |
| Dementia | No | 3385 (84.62) | 3380 (84.50) |
| | Yes | 615 (15.38) | 620 (15.50) |
| Outcome (not included in matching) | | | |
| Acute Kidney Injury | No | 2980 (74.50) | 2945 (73.62) |
| | Yes | 1020 (25.50) | 1055 (26.38) |

**Table S9 –** Propensity matched secondary outcomes after excluding those who died

| Outcome | Patients who were alive and had available data for matching (1:1) | Effect estimate (Odds ratio, 95%CI) |
|---|---|---|
| No NSAIDs (Reference) | | 1 (reference level) |
| Critical Care - NSAIDs | (3376:3376) | 0.91 (0.79 to 1.06, p = 0.243) |
| Invasive ventilation - NSAIDs | (3350:3350) | 0.84 (0.67 to 1.07, p = 0.151) |
| Non-invasive ventilation – NSAIDs | (3338:3338) | 0.99 (0.80 to 1.22, p = 0.896) |
| Oxygen – NSAIDs | (3340:3340) | 0.96 (0.85 to 1.08, p = 0.517) |
| AKI - NSAIDs | (2915:2915) | 0.97 (0.84 to 1.13, p = 0.712) |

AKI – Acute kidney injury, 95%CI – 95% confidence interval, NSAIDs – non-steroidal anti-inflammatory drugs

**Table S10** – Effect of different NSAIDs on mortality in patients with COVID-19 after adjustment for explanatory variables in an unmatched cohort.

| | | Died | Alive | OR (univariable) | OR (multilevel) |
|---|---|---|---|---|---|
| NSAID type | No NSAIDs | 42042 (67.4) | 20372 (32.6) | - | - |
| | COX-2 Inhibitor | 82 (75.9) | 26 (24.1) | 0.65 (0.41-1.00, p=0.060) | 1.06 (0.64-1.77, p=0.822) |
| | Diclofenac/ Ketorolac /Naproxen | 186 (68.1) | 87 (31.9) | 0.97 (0.74-1.24, p=0.786) | 1.10 (0.81-1.50, p=0.529) |
| | Ibuprofen (or similar propionic acid derivative) | 681 (74.9) | 228 (25.1) | 0.69 (0.59-0.80, p<0.001) | 0.88 (0.73-1.06, p=0.188) |
| | Mixed NSAIDs | 551 (74.4) | 190 (25.6) | 0.71 (0.60-0.84, p<0.001) | 1.14 (0.93-1.39, p=0.195) |
| | Oxicam | 91 (64.1) | 51 (35.9) | 1.16 (0.82-1.62, p=0.406) | 1.25 (0.82-1.89, p=0.302) |
| Age on admission (years) | <50 | 9408 (94.7) | 530 (5.3) | - | - |
| | 50-69 | 15526 (79.5) | 4008 (20.5) | 4.58 (4.17-5.04, p<0.001) | 3.81 (3.38-4.30, p<0.001) |
| | 70-79 | 10181 (63.2) | 5918 (36.8) | 10.32 (9.41-11.34, p<0.001) | 8.14 (7.22-9.18, p<0.001) |
| | 80+ | 14395 (54.5) | 12024 (45.5) | 14.83 (13.55-16.25, p<0.001) | 12.14 (10.78-13.67, p<0.001) |
| Sex at Birth | Female | 22647 (71.9) | 8862 (28.1) | - | - |
| | Male | 26823 (66.4) | 13583 (33.6) | 1.29 (1.25-1.34, p<0.001) | 1.42 (1.36-1.48, p<0.001) |
| Chronic cardiac disease | No | 33429 (73.7) | 11959 (26.3) | - | - |
| | Yes | 12959 (58.7) | 9107 (41.3) | 1.96 (1.90-2.03, p<0.001) | 1.14 (1.09-1.19, p<0.001) |
| Chronic pulmonary disease (not asthma) | No | 39145 (71.0) | 16007 (29.0) | - | - |
| | Yes | 7128 (59.3) | 4891 (40.7) | 1.68 (1.61-1.75, p<0.001) | 1.24 (1.18-1.31, p<0.001) |
| Chronic kidney disease | No | 39354 (71.5) | 15683 (28.5) | - | - |
| | Yes | 6773 (56.8) | 5154 (43.2) | 1.91 (1.83-1.99, p<0.001) | 1.27 (1.21-1.34, p<0.001) |
| Obesity (as defined by clinical staff) | No | 36603 (69.0) | 16429 (31.0) | - | - |
| | Yes | 5194 (72.5) | 1973 (27.5) | 0.85 (0.80-0.89, p<0.001) | 1.21 (1.13-1.29, p<0.001) |
| Diabetes | No Diabetes | 35006 (70.6) | 14603 (29.4) | - | - |
| | Diabetes with complications | 3088 (64.6) | 1695 (35.4) | 1.32 (1.24-1.40, p<0.001) | 1.05 (0.97-1.14, p=0.191) |
| | Diabetes without complications | 6899 (64.2) | 3844 (35.8) | 1.34 (1.28-1.40, p<0.001) | 1.19 (1.13-1.25, p<0.001) |
| Rheumatologic disorder | No | 40789 (69.6) | 17825 (30.4) | - | - |
| | Yes | 4922 (64.6) | 2692 (35.4) | 1.25 (1.19-1.32, p<0.001) | 0.94 (0.89-1.00, p=0.070) |

NSAIDs – Nonsteroidal anti-inflammatory drugs, COX – Cyclooxygenase.

**Table S11 -** Sensitivity analysis of effect of Ibuprofen on in-hospital mortality, compared with no NSAIDs.

| Dependent | Patients who were alive and had available data for matching (1:1) | Effect estimate (Odds ratio, 95%CI) |
|---|---|---|
| No NSAIDs (reference) | | 1 (reference level) |
| Ibuprofen | (721:721) | 0.90 (0.71 to 1.13, p = 0.359) |

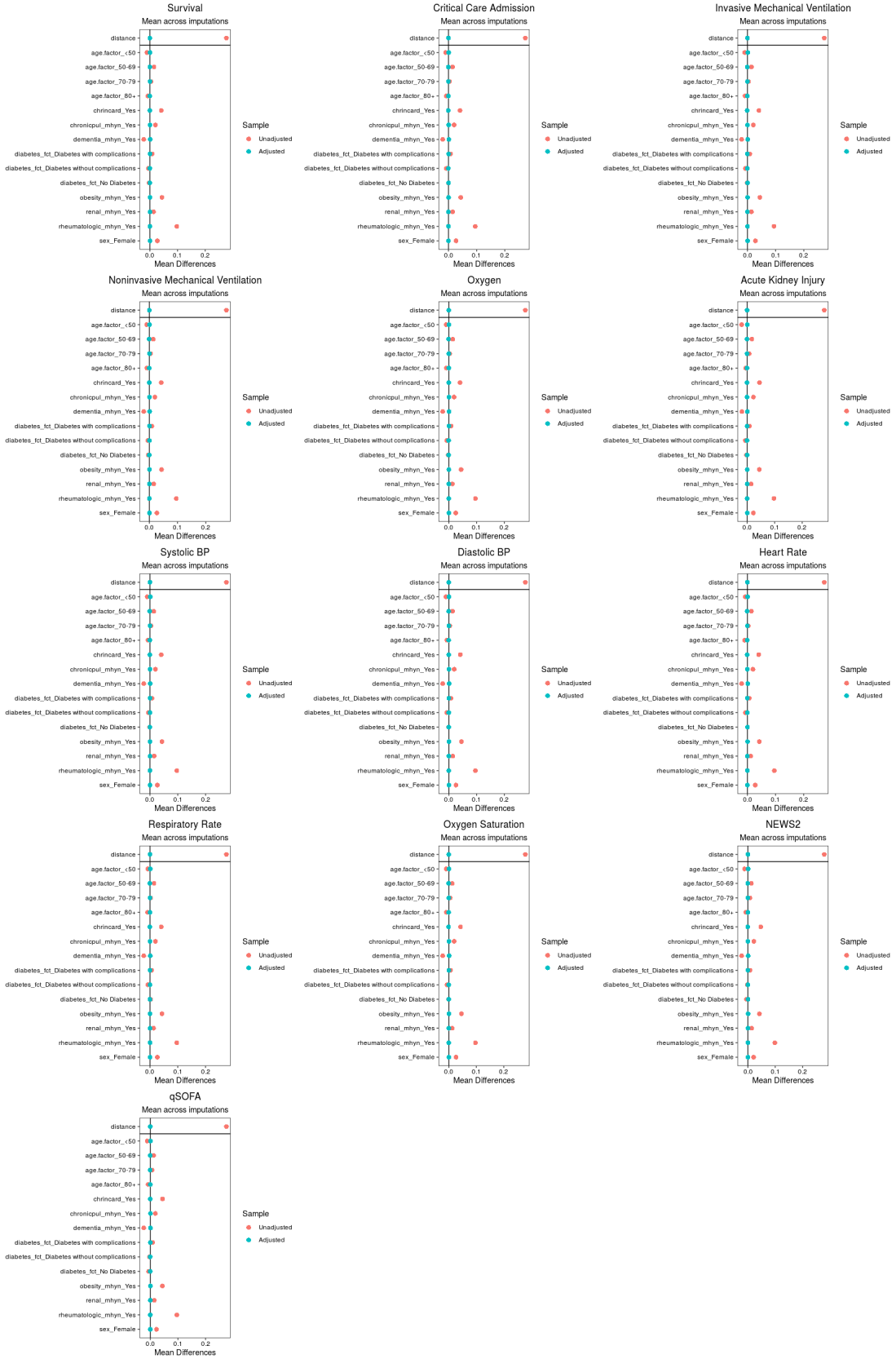
NSAIDs – Nonsteroidal anti-inflammatory drugs, 95% CI – 95% Confidence Interval.

**Table S12 –** Sensitivity analysis of effect of Ibuprofen on in-hospital mortality, compared with other NSAIDs.

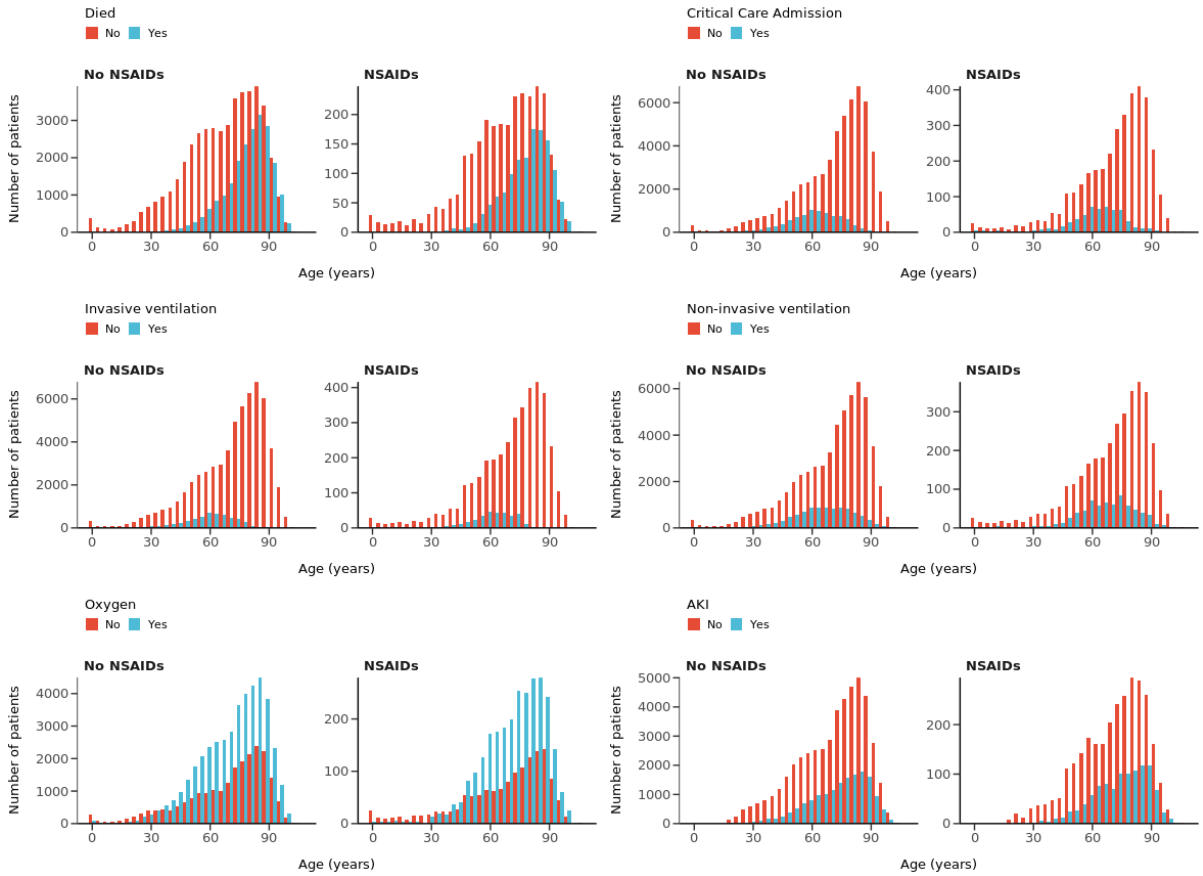
| Outcome | Patients who were alive and had available data for matching (1:1) | Effect estimate (Odds ratio, 95%CI) |
|---|---|---|
| Other NSAIDs (reference) | | 1 (reference level) |
| Ibuprofen | (908:908) | 0.82 (0.66 to 1.03, p = 0.082) |

NSAIDs – Nonsteroidal anti-inflammatory drugs, 95% CI – 95% Confidence Interval.

**Supplementary Figure 1 –** Balance plots after imputation and propensity score matching



**Supplementary Figure 2 –** Outcomes in the unmatched cohort by age and NSAID use (y-axes scaled to reflect number of patients in each group).




NSAIDs – Non-steroidal anti-inflammatory drugs.

**Authorship supplement (for ISARIC4C investigators)**

Consortium Lead Investigator: J Kenneth Baillie. Chief Investigator: Malcolm G Semple. Co-Lead Investigator: Peter JM Openshaw. ISARIC Clinical Coordinator: Gail Carson. Co-Investigator: Beatrice Alex, Benjamin Bach, Wendy S Barclay, Debby Bogaert, Meera Chand, Graham S Cooke, Annemarie B Docherty, Jake Dunning, Ana da Silva Filipe, Tom Fletcher, Christoper A Green, Ewen M Harrison, Julian A Hiscox, Antonia Ying Wai Ho, Peter W Horby, Samreen Ijaz, Saye Khoo, Paul Klenerman, Andrew Law, Wei Shen Lim, Alexander J Mentzer, Laura Merson, Alison M Meynert, Mahdad Noursadeghi, Shona C Moore, Massimo Palmarini, William A Paxton, Georgios Pollakis, Nicholas Price, Andrew Rambaut, David L Robertson, Clark D Russell, Vanessa Sancho-Shimizu, Janet T Scott, Thushan de Silva, Louise Sigfrid, Tom Solomon, Shiranee Sriskandan, David Stuart, Charlotte Summers, Richard S Tedder, Emma C Thomson, AA Roger Thompson, Ryan S Thwaites, Lance CW Turtle, Maria Zambon. Project Manager: Hayley Hardwick, Chloe Donohue, Ruth Lyons, Fiona Griffiths, Wilna Oosthuyzen. Data Analyst: Lisa Norman, Riinu Pius, Thomas M Drake, Cameron J Fairfield, Stephen R Knight, Kenneth A Mclean, Derek Murphy, Catherine A Shaw. Data and Information System Manager: Jo Dalton, Michelle Girvan, Egle Saviciute, Stephanie Roberts, Janet Harrison, Laura Marsh, Marie Connor, Sophie Halpin, Clare Jackson, Carrol Gamble. Data Integration and Presentation: Gary Leeming, Andrew Law, Murray Wham, Sara Clohisey, Ross Hendry, James Scott-Brown. Material Management: William Greenhalf, Victoria Shaw, Sara McDonald. Patient Engagement: Seán Keating. Outbreak Laboratory Staff and Volunteers: Katie A. Ahmed, Jane A Armstrong, Milton Ashworth, Innocent G Asiimwe, Siddharth Bakshi, Samantha L Barlow, Laura Booth, Benjamin Brennan, Katie Bullock, Benjamin WA Catterall, Jordan J Clark, Emily A Clarke, Sarah Cole, Louise Cooper, Helen Cox, Christopher Davis, Oslem Dincarslan, Chris Dunn, Philip Dyer, Angela Elliott, Anthony Evans, Lorna Finch, Lewis WS Fisher, Terry Foster, Isabel Garcia-Dorival, William Greenhalf, Philip Gunning, Catherine Hartley, Rebecca L Jensen, Christopher B Jones, Trevor R Jones, Shadia Khandaker, Katharine King, Robyn T. Kiy, Chrysa Koukorava, Annette Lake, Suzannah Lant, Diane Latawiec, Lara Lavelle-Langham, Daniella Lefteri, Lauren Lett, Lucia A Livoti, Maria Mancini, Sarah McDonald, Laurence McEvoy, John McLauchlan, Soeren Metelmann, Nahida S Miah, Joanna Middleton, Joyce Mitchell, Shona C Moore, Ellen G

Murphy, Rebekah Penrice-Randal, Jack Pilgrim, Tessa Prince, Will Reynolds, P. Matthew Ridley, Debby Sales, Victoria E Shaw, Rebecca K Shears, Benjamin Small, Krishanthi S Subramaniam, Agnieska Szemiel, Aislynn Taggart, Jolanta Tanianis-Hughes, Jordan Thomas, Erwan Trochu, Libby van Tonder, Eve Wilcock, J. Eunice Zhang, Lisa Flaherty, Nicole Maziere, Emily Cass, Alejandra Doce Carracedo, Nicola Carlucci, Anthony Holmes, Hannah Massey. Edinburgh Laboratory Staff and Volunteers: Lee Murphy, Nicola Wrobel, Sarah McCafferty, Kirstie Morrice, Alan MacLean. Local Principal Investigators: Kayode Adeniji, Daniel Agranoff, Ken Agwuh, Dhiraj Ail, Erin L. Aldera, Ana Alegria, Brian Angus, Abdul Ashish, Dougal Atkinson, Shahedal Bari, Gavin Barlow, Stella Barnass, Nicholas Barrett, Christopher Bassford, Sneha Basude, David Baxter, Michael Beadsworth, Jolanta Bernatoniene, John Berridge, Nicola Best, Pieter Bothma, David Chadwick, Robin Brittain-Long, Naomi Bulteel, Tom Burden, Andrew Burtenshaw, Vikki Caruth, David Chadwick, Duncan Chambler, Nigel Chee, Jenny Child, Srikanth Chukkambotla, Tom Clark, Paul Collini, Catherine Cosgrove, Jason Cupitt, Maria-Teresa Cutino-Moguel, Paul Dark, Chris Dawson, Samir Dervisevic, Phil Donnison, Sam Douthwaite, Ingrid DuRand, Ahilanadan Dushianthan, Tristan Dyer, Cariad Evans, Chi Eziefula, Chrisopher Fegan, Adam Finn, Duncan Fullerton, Sanjeev Garg, Sanjeev Garg, Atul Garg, Effrossyni Gkrania-Klotsas, Jo Godden, Arthur Goldsmith, Clive Graham, Elaine Hardy, Stuart Hartshorn, Daniel Harvey, Peter Havalda, Daniel B Hawcutt, Maria Hobrok, Luke Hodgson, Anil Hormis, Michael Jacobs, Susan Jain, Paul Jennings, Agilan Kaliappan, Vidya Kasipandian, Stephen Kegg, Michael Kelsey, Jason Kendall, Caroline Kerrison, Ian Kerslake, Oliver Koch, Gouri Koduri, George Koshy, Shondipon Laha, Steven Laird, Susan Larkin, Tamas Leiner, Patrick Lillie, James Limb, Vanessa Linnett, Jeff Little, Mark Lyttle, Michael MacMahon, Emily MacNaughton, Ravish Mankregod, Huw Masson, Elijah Matovu, Katherine McCullough, Ruth McEwen, Manjula Meda, Gary Mills, Jane Minton, Mariyam Mirfenderesky, Kavya Mohandas, Quen Mok, James Moon, Elinoor Moore, Patrick Morgan, Craig Morris, Katherine Mortimore, Samuel Moses, Mbiye Mpenge, Rohinton Mulla, Michael Murphy, Megan Nagel, Thapas Nagarajan, Mark Nelson, Matthew K. O'Shea, Igor Otahal, Marlies Ostermann, Mark Pais, Selva Panchatsharam, Danai Papakonstantinou, Hassan Paraiso, Brij Patel, Natalie Pattison, Justin Pepperell, Mark Peters, Mandeep Phull, Stefania Pintus, Jagtur Singh Pooni, Frank Post, David Price, Rachel Prout, Nikolas

Rae, Henrik Reschreiter, Tim Reynolds, Neil Richardson, Mark Roberts, Devender Roberts, Alistair Rose, Guy Rousseau, Brendan Ryan, Taranprit Saluja, Aarti Shah, Prad Shanmuga, Anil Sharma, Anna Shawcross, Jeremy Sizer, Manu Shankar-Hari, Richard Smith, Catherine Snelson, Nick Spittle, Nikki Staines, Tom Stambach, Richard Stewart, Pradeep Subudhi, Tamas Szakmany, Kate Tatham, Jo Thomas, Chris Thompson, Robert Thompson, Ascanio Tridente, Darell Tupper-Carey, Mary Twagira, Andrew Ustianowski, Nick Vallotton, Lisa Vincent-Smith, Shico Visuvanathan, Alan Vuylsteke, Sam Waddy, Rachel Wake, Andrew Walden, Ingeborg Welters, Tony Whitehouse, Paul Whittaker, Ashley Whittington, Padmasayee Papineni, Meme Wijesinghe, Martin Williams, Lawrence Wilson, Sarah Cole, Stephen Winchester, Martin Wiselka, Adam Wolverson, Daniel G Wooton, Andrew Workman, Bryan Yates, Peter Young.

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